

## ***Remarks***

### ***I. Status of the Claims***

Claims 1, 2, 4, 5, 10 and 16 are pending in the application, with claim 1 being the sole independent claim. Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

### ***II. Summary of the Office Action***

In the Office Action dated June 2, 2004, the Examiner maintained five rejections that had been made in the previous Office Action. Applicants respectfully offer the following remarks in traversal of each of these rejections.

### ***III. The Rejections Under 35 U.S.C. § 112, first paragraph***

#### ***A. Enablement***

At pages 2-10, paragraph 4 of the Office Action, the Examiner has maintained the rejection of claims 1, 2, 4-5, 10 and 16 under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner states that it would require undue experimentation by one skilled in the art to practice the claimed invention. Applicants respectfully traverse the rejection.

#### ***1. The Examiner's Burden***

The Examiner bears the initial burden of proving that a specification is non-enabling. *See In re Marzocchi*, 169 USPQ 367 (C.C.P.A. 1971). A specification is presumed to be enabling unless the Examiner provides acceptable objective evidence or sound scientific reasoning showing that it would require undue experimentation for one

of ordinary skill in the art to make and use the claimed invention. *See Id.*; *see also In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993). In the present case, the Examiner's burden has not been satisfied.

In maintaining this rejection in the final Office Action, the Examiner has based this rejection on the same points that were made in the non-final Office Action dated November 7, 2003. In their reply submitted on March 8, 2004, Applicants provided specific grounds of rebuttal of each of these contentions, demonstrating why the enablement rejection was legally and factually baseless. However, instead of specifically rebutting Applicants' arguments in the present Office Action, the Examiner has simply reiterated *verbatim* the points made in the previous non-final Office Action. Such an approach does not advance prosecution.

Moreover, Applicants respectfully remind the Examiner that "[w]here the applicant traverses any rejection, the examiner should, if he or she repeats the rejection, take note of the applicant's argument and answer the substance of it." MPEP § 707.07(f) (February 2003). Clearly, this guidance of the MPEP has not been followed in issuing the present final Office Action. Based solely on this reason, Applicants respectfully contend that the present Office Action is improper, and should be reconsidered and withdrawn in its entirety. However, should the Examiner not be inclined to do so, Applicants offer the following additional remarks regarding this rejection.

In the Office Action dated November 7, 2003, and in the present final Office Action, the Examiner first contends that the specification does not sufficiently enable the method of modulating the immune system of any animal by contacting any antigen-presenting cell with an effective amount of any retinoid and any cytokine for treating any disease. Applicants respectfully assert that the Examiner's use of the phrase "for treating

*any* disease" is a mischaracterization of the presently claimed invention. The specification states that the methods of the presently claimed invention may be used to treat ". . . a physical disorder that may be delayed, prevented, cured or otherwise treated by differentially modulating immune system function . . . ." (*see, e.g.*, Specification at page 22). Therefore, it is improper to base the present rejection on the notion that a treatment for "any disease" is not enabled by the present specification -- Applicants are not claiming the treatment of *any* disease, but instead a subset of physical disorders with defined characteristics. Indeed, the use of such methods to treat such diseases is specifically disclosed in the present specification, *e.g.*, at pages 58-72. Therefore, Applicants submit that the full scope of the claimed methods and compositions could be practiced by those of ordinary skill in the art without undue experimentation. Additionally, Applicants assert that the Examiner has not provided a sufficient explanation or sound scientific reasoning as to why the specification would not enable the claimed invention; therefore, the Examiner has not established a *prima facie* case of nonenablement.

## **2.      *What is Known in the Art***

At pages 4 and 8 of the present Office Action, the Examiner extends the above-noted reliance on the word "any," by stating that the specification does not teach how to make "any" pan-RXR agonist, "any" RAR antagonist, "any" Compound V, "any" Compound II, "any" Compound VIII and/or "any" ester or prodrug thereof. The Examiner goes on to state that the specification also fails to teach how to make "any" analog or derivatives of tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) or interleukin-1 $\beta$  (IL-1 $\beta$ ) for the

claimed method of modulating the immune system of an animal. Applicants respectfully disagree with these contentions.

In order to enable a claimed invention, a specification need not teach, and preferably omits, information that is well-known to those of ordinary skill in the art. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986); *Lindemann Maschinenfabrik v. American Hoist and Derrick*, 730 F.2d 1452, 1463 (Fed. Cir. 1984); *In re Wands*, 8 USPQ2d 1400, 1402 (Fed. Cir. 1988). In addition, one of ordinary skill in the art is deemed to know not only what is considered well-known, but also where to search for any needed starting materials. *See In re Howarth*, 210 USPQ 689, 692, (CCPA 1981). Under these standards, the present specification fully enables the presently claimed invention.

Pages 38-58 of the specification disclose not only a number of RXR and RAR agonists and antagonists, but also the sources from which information about these compounds can be obtained. Specifically, the specification discloses sources where the structures and/or methods of synthesis can be found for Compounds I, II, III, IV, V, VI, VII, VIII and SR11237 (*see* Specification, *e.g.*, page 57, paragraph 103 and page 58, Table 1b). The specification also discloses a general method for synthesizing Compound III (*see* Specification page 54, paragraph 100, through page 55, paragraph 101).

Applicants note that Compounds II, V and VIII (as well as the other compounds having specific roman numeral designations that are disclosed in the present specification) are *specific* compounds having *specific* structures, that are fully disclosed in the present specification either explicitly or through incorporation by reference of the above-noted sources. Applicants therefore are somewhat mystified by the Examiner's statements in the Office Action that the specification does not teach how to make and use

"any" Compound II, V or VIII -- since these are individual compounds, and the structure of each is disclosed in the specification, the Examiner's statements regarding the alleged nonenablement of these and the other specific compounds are simply incorrect.

Similarly, the present specification discloses a number ways in which cytokines, both natural and synthetic, can be procured (*see, e.g.*, Specification at pages 72-73, paragraph 137). These include isolation from natural sources such as activated monocytes or macrophages, production using recombinant DNA techniques familiar to the ordinarily skilled artisan, acquisition from commercial sources and synthesis according to standard methods of protein synthesis. Both nucleotide sequences and three-dimensional protein structures for cytokines are well known in the art. With this knowledge, fully active variants, analogues and derivatives of cytokines can be produced and used in the method of the invention, and need not be taught by the specification in order to enable the claimed invention. Hence, as was the case for the specific compounds discussed above, the Examiner's contention that the present specification does not enable one of ordinary skill to use "any" cytokine is simply incorrect.

Additionally, at pages 6 and 9 of the present Office Action, the Examiner states that given the allegedly indefinite number of undisclosed pan-RXR agonists, RAR antagonists, the diverse functions of each agonist, antagonist, analog and derivatives of TNF $\alpha$  and IL-1 $\beta$  through distinct receptor pathways, it is unpredictable which one of the undisclosed pan-RXR agonists, RAR antagonists, TNF $\alpha$  and IL-1 $\beta$  analogs and derivatives thereof would maintain the same structure and function and would be useful for modulating the immune system for treating any disease. To support this contention, the Examiner cites Stryer *et al.*, Ngo *et al.*, Attwood, Skolnick *et al.* and Geissmann *et al.* for the proposition that any changes to a protein, such as those found in a derivative or

analogue, make the function of that protein unpredictable. Applicants respectfully disagree with these contentions.

The Examiner's attention is again directed to pages 38-58 of the present specification, which describe a large number of retinoids, including RAR agonists (selective for  $\alpha$ ,  $\beta$  and/or  $\gamma$  RARs, or pan RAR agonists), RXR agonists and RAR antagonists. For each of these groups both general structures and specific examples are disclosed (*see, e.g.*, Specification at page 40). Moreover, the present specification provides detailed disclosure of assays useful in determining the function of a given retinoid analogue (*see, e.g.* Specification at pages 32, 34-35, 36, 58-70, and throughout the Examples). Hence, the present specification is replete with information relating to the structure and function of retinoids suitable for use in the claimed invention. Again, as was the case for the specific compounds and cytokines discussed above, the Examiner's contention that the present specification does not enable one of ordinary skill to make and use "any" retinoid is simply incorrect.

Finally, in dismissing (without specifically rebutting) Applicants' replies to these same contentions in the previous Office Action, the Examiner states at page 6 of the present Office Action that the claims are not drawn to compounds. This comment is particularly disingenuous and beside the point, especially in view of the Examiner's statements noted above that the present specification does not enable "any" Compounds II, V and VIII, "any" cytokine, "any" retinoid, etc. The Examiner cannot have it both ways -- *i.e.*, enablement rejections of the present method claims cannot be based on whether or not specific compounds used in such methods are enabled, while then refusing to consider arguments addressing the enablement of such methods that are *also* based on the enablement of such compounds. Such an approach -- an offhand dismissal

of arguments that specifically rebut the stated grounds of rejection -- does not advance prosecution and is not in line with the guidance of MPEP § 707.07(f). More importantly, such an approach does not meet the Office's burden of establishing a *prima facie* case of nonenablement, as required under *Marzocchi* and *Wright*.

Therefore, in view of the teachings of the present specification and information that is known in the art (which, under *Hybritech*, *Lindemann Maschinenfabrik*, *Wands*, and *Howarth*, need not be taught in, and preferably is omitted from, the present specification), one of ordinary skill would be able to make and use retinoids, cytokines and antigen-presenting cells as claimed in claims 1-2, 4-5, 10 and 16 with a reasonable expectation of success and without undue experimentation. Hence, the present specification fully enables claims 1-2, 4-5, 10 and 16 as currently presented.

### **3.     *Need for Working Examples***

At page 6 and page 9-10 of the Office Action, the Examiner contends that "even if the claimed method is limited to [] specific retinoids . . . there is no in vivo working example demonstrating that the claimed method is effective for modulating the immune system for treating any disease." The Examiner gives no further reasoning beyond that provided in the Office Action of November 7, 2003, to support such a contention. Hence, this rejection is again based on a reiteration of a prior line of reasoning for the same rejection, to which Applicants have already replied. However, the Examiner has again simply dismissed Applicants' remarks on this issue, without specifically addressing them, which again is contrary to the guidelines established in the MPEP. Nonetheless, Applicants offer the following remarks concerning this rejection, and request that the Examiner specifically consider and respond to these remarks in the next communication.

Applicants again respectfully assert that the Examiner's contention regarding the lack of *in vivo* data or working examples is irrelevant to the level of enablement provided by the present specification. In order to enable a claimed invention, a specification need not disclose working examples. "Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *In re Wright*, 27 USPQ2d 1510, 1561 (Fed. Cir. 1999); *see also In re Borkowski*, 422 F.2d 904, 908 (C.C.P.A. 1970). Hence, whether or not the present specification provides working examples (or indeed, *any* examples) is not germane to the enablement of the claimed invention.

The Examiner admits, at page 2 of the present Office Action, that the present specification discloses a method for inhibiting retinol-induced apoptosis of dendritic cells, as well as a method of enhancing antigen presentation in dendritic cells. Coupled with the disclosure of routine methods of testing (*see* Specification at pages 58-72) to determine the effects of various retinoids, cytokines and antigen-presenting cells in the methods of the invention, this disclosure meets the standards for enablement under 35 U.S.C. § 112, first paragraph, as interpreted under *Wright*. Hence, by the Examiner's own admission, the present specification fully enables claims 1-2, 4-5, 10 and 16 as currently presented.

If, instead, the Examiner is basing the present rejection on some notion that *in vivo* working examples must be shown, and that the *in vitro* results presented in the specification are insufficient to enable *in vivo* methods, Applicants respectfully disagree. There is no requirement for clinical or *in vivo* data to prove that an application is in compliance with 35 U.S.C. § 112, first paragraph. In fact, the description of *in vitro*



and/or animal testing has been held to enable claims to *in vivo* therapeutic compositions and methods of their use. To this end, the Federal Circuit has stated that:

In vitro testing, in general, is relatively less complex, less time consuming, and less expensive than in vivo testing. Moreover, in vitro results with respect to the particular pharmacological activity are generally predictive of in vivo results, i.e., there is a reasonable correlation there between. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are.

*Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985).

The present specification clearly describes methods for preparation and use of the claimed invention *in vitro* (see e.g., Specification at pages 87-90). Under *Cross*, one of ordinary skill would thus recognize that the *in vitro* testing described in the present specification would be "generally predictive of *in vivo* test results," *Cross*, 753 F.2d at 1050, and thus would have a reasonable expectation that the claimed methods would be successful for the claimed *in vivo* methods. Thus, any contention to the contrary is legally and factually erroneous.

#### **4. Undue Experimentation under Wands**

Finally, at page 6, paragraph 6 of the Office Action, the Examiner concludes with the broad generalization that "it would require undue experimentation of [*sic*] one of ordinary skill in the art to practice the claimed invention." However, the Examiner gives no further reasoning beyond that provided in the Office Action of November 7, 2003, for such a broad conclusory statement. Applicants again respectfully disagree with this contention.

As discussed in detail above, one of ordinary skill could readily practice the presently claimed invention without resorting to undue experimentation. The

Examiner has provided no permissible reasons for questioning this statement. Hence, under *Marzocchi* and *Wright*, the present specification *must* be taken as enabling the presently claimed invention, since a *prima facie* case of nonenablement has not been established.

Moreover, it is respectfully requested that in reconsidering this rejection, the Examiner also keep in mind that the question of undue experimentation is a matter of degree, and "the key word is 'undue,' not 'experimentation.'" *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), quoting *In re Angstadt*, 190 USPQ 214, 219 (C.C.P.A. 1976). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation not be unduly extensive. *PPG Indus., Inc. v. Guardian Indus. Corp.*, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996), citing *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 224 USPQ 409, 413 (Fed. Cir. 1984). Furthermore, the test of whether an amount of experimentation is undue is not merely quantitative; a considerable amount of experimentation is permissible, if it is merely routine (*i.e.*, uses methods known to those of ordinary skill in the relevant arts), or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *See PPG Indus.*, 37 USPQ2d at 1623, citing *Ex parte Jackson*, 217 USPQ 804, 807 (Bd. Pat. App. & Inter. 1982).

As noted above, pages 58-72 of the present specification disclose a number of methods to screen candidate compounds for their usefulness in the claimed invention. For example, the specification discloses a screening method in which a first antigen-presenting cell is treated with candidate compounds, while a second antigen-presenting

cell is left untreated, but incubated under identical conditions, to determine the abilities of the compounds to activate or induce/delay/prevent apoptosis in the treated cell. (*see* page 61, paragraph 119). Therefore, the functionality of a particular retinoid, and/or cytokine in modulating the immune system, can be routinely determined by one skilled in the art using any number of assays disclosed in the specification without the need for undue experimentation. The Examiner has offered no specific reasoning that would rebut this fact, and has instead relied upon a broad, unsupported conclusion that undue experimentation would be required. Thus, the Office's burden of proving nonenablement has not been met, and consequently, the present specification fully enables claims 1-2, 4-5, 10 and 16 as currently presented.

***B. Written Description***

At page 10, paragraph 5 of the final Office Action, the Examiner has maintained the rejection of claims 1, 2, 4-5, 10 and 16 under 35 U.S.C. § 112, first paragraph for lack of written description. The Examiner states that the rejected claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor had possession of the claimed invention. The Examiner's reasoning for the written description rejection is essentially the same as the reasoning for the enablement rejection as discussed above. Applicants respectfully traverse the rejection.

In maintaining this rejection in the final Office Action, the Examiner has based this rejection on the same points that were made in the non-final Office Action dated November 7, 2003. In their reply submitted on March 8, 2004, Applicants provided specific grounds of rebuttal of each of these contentions, demonstrating why the written

description rejection was legally and factually baseless. However, instead of specifically rebutting Applicants' arguments in the present Office Action, the Examiner has simply reiterated *verbatim* the points made in the previous non-final Office Action. As noted above, such an approach does not advance prosecution and is contrary to the clear guidance of MPEP § 707.07(f), which notes that the Examiner should answer the *substance* of Applicants' arguments. Based solely on this reason, Applicants again respectfully contend that the present Office Action is improper, and should be reconsidered and withdrawn in its entirety. However, should the Examiner not be inclined to do so, Applicants offer the following additional remarks regarding this rejection.

Applicants respectfully remind the Examiner that "[a]dequate description under the first paragraph of 35 U.S.C. 112 does not require *literal* support for the claimed invention." That is, "[T]he observation of a lack of literal support does not, in and of itself, establish a *prima facie* case for lack of adequate descriptive support under the first paragraph of 35 U.S.C. 112." *Ex parte Parks*, 30 USPQ2d 1234, 1236 (Bd. Pat. App. Int. 1994). Instead, the written description requirement of 35 U.S.C. § 112, first paragraph, is met "if the originally-filed disclosure would have conveyed to one having ordinary skill in the art that an [applicant] had possession of the concept of what is claimed," *id.*, *i.e.*, "[i]f a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification . . . ." *In re Alton*, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996). An applicant is not required to disclose or provide a working example of every species of a given genus in order to meet the written description requirement of 35 U.S.C. § 112 (*see Parks and Alton*), and subject

matter that "might fairly be deduced from the original application" is considered to be described in the application as filed. *Acme Highway Prod. Corp. v. D.S. Brown Co.*, 431 F.2d 1074, 1080 (6th Cir. 1970) (citations omitted), *cert. denied*, 401 U.S. 956 (1971), followed by *Westphal v. Fawzi*, 666 F.2d 575, 577 (C.C.P.A. 1981). Moreover, "[a] description of a genus . . . may be achieved by means of recitation of a representative number of [species] . . . falling within the scope of the genus . . . ." *Regents of Univ. of Calif. v. Eli Lilly & Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997).

As detailed above, the present specification describes the structures of a large number of retinoids, including RAR agonists (selective for  $\alpha$ ,  $\beta$  and/or  $\gamma$  RARs, or pan RAR agonists), RXR agonists and RAR antagonists. Citations for descriptions and/or methods of synthesizing these agonists and antagonists are also disclosed. Additionally, the specification discloses a number of methods to screen candidate retinoid and cytokine compounds and antigen-presenting cells for their usefulness in the presently claimed methods. Specifically, these methods are used to determine which specific combinations of retinoid and cytokine compounds will have a stimulating or inhibitory effect on antigen-presenting cells. As detailed above, because both nucleotide sequences and three-dimensional protein structures for cytokines are well known in the art, sufficient written description exists in the specification such that fully active variants, analogues and derivatives of cytokines can be produced and used in the method of the invention. Finally, the specification discloses a method for inhibiting retinol-induced apoptosis of Langerhans cells, as well as a method of enhancing antigen presentation in Langerhans cells. Hence, under the standards set forth in *Parks*, *Alton*, *Acme* and *Eli Lilly*, the present specification provides sufficient written description to convey to one of

ordinary skill that Applicants had possession of the full scope of the invention as claimed in claims 1-2, 4-5, 10 and 16.

**C. Summary**

Therefore, Applicants respectfully assert that the present specification is sufficiently enabling such that one of ordinary skill would be able to make and use the invention with a reasonable expectation of success and without undue experimentation. Additionally, the specification provides sufficient written description to convey to one of ordinary skill that Applicants had possession of the full scope of the claimed invention upon filing of the application. Moreover, the Examiner has not specifically addressed the substance of Applicants' arguments regarding these same rejections that were made in the March 8, 2004, reply, contrary to the clear guidance of the MPEP. In view of the foregoing remarks, Applicants respectfully request that the rejections under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

**IV. The Rejection Under 35 U.S.C. § 102(b) Over Trinchieri *et al.***

At page 10, paragraph 13 of the Office Action, the Examiner has maintained the rejection of claims 1 and 10 under 35 U.S.C. § 102(b) as being anticipated by Trinchieri *et al.* The Examiner again contends that Trinchieri *et al.* teach a method of modulating the immune system of an animal by affecting the physiology of undifferentiated promyelocytic HL-60 cells with a retinoid and a cytokine. Applicants respectfully traverse this rejection and the contentions upon which it is based.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v.*

*Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). This requirement is not met by the disclosure of Trinchieri *et al.*

Claim 1 recites "a method of modulating the immune system of an animal by affecting the physiology of an antigen-presenting cell in said animal, comprising contacting said antigen-presenting cell with an effective amount of at least one retinoid and an effective amount of at least one cytokine, under conditions whereby the physiology of said antigen-presenting cell is affected." Trinchieri *et al.* studied the growth and differentiation of HL-60 cells using retinoic acid and tumor necrosis factor. HL-60 cells are a human myeloid cell line (*See Trinchieri et al.* p. 1218). As one of ordinary skill in the art would understand, HL-60 cells are undifferentiated promyelocytic cells that do not possess antigen-presenting capabilities. As one of ordinary skill in the art would also understand, just because a cell is phagocytic does not mean *a priori* that it is capable of antigen presentation. For example, single-celled amoebas are phagocytic, but are not considered "antigen-presenting cells" as that term is defined in the present specification. Indeed, even the initial report of the establishment and characterization of the HL-60 cell line did not indicate that HL-60 cells are antigen-presenting cells (*see Gallagher et al. Blood. 54(3):713-733 (1979)*, of record as Doc. No. AT75). Specifically, despite conducting functional studies to characterize this cell line, Gallagher *et al.* do not disclose that HL-60 cells have the ability to present antigen, which is the very characteristic by which an "antigen-presenting cell" is defined. The Examiner also has provided no objective information or sound scientific reasoning, from the disclosures of Gallagher, Trinchieri or any other reference, which would support a contention that HL-60 cells are antigen-presenting cells.

Instead, the Examiner somehow appears to conflate undifferentiated HL-60 cells and the differentiated cells that are obtained after treatment of HL-60 cells with retinoids and TNF- $\alpha$  as disclosed in Trinchieri (*see* Office Action at page 15, third full paragraph). Such a conflation is wholly unfounded. The present claims are not drawn to the treatment of cells that *might acquire* antigen-presenting capabilities upon treatment with retinoids and cytokines. Instead, the cells that are treated with retinoids and cytokines by the present methods *already are* antigen-presenting cells. Trinchieri does not indicate that HL-60 cells are antigen-presenting cells *prior* to being treated with retinoids and cytokines. Indeed, Trinchieri does not even indicate that HL-60 cells are antigen-presenting cells *after* treatment with such agents, instead stating that these cells become differentiated and obtain certain features of a monocytic/macrophage phenotype *without* stating that they become capable of antigen presentation. At best, Trinchieri shows that the treatment of cells that are *not* antigen-presenting cells with retinoids/cytokines can differentiate the cells into phagocytic cells which are not necessarily antigen-presenting cells. As noted above, the presently claimed invention is drawn to the treatment of antigen-presenting cells with combinations of retinoids and cytokines. In contrast, Trinchieri only discloses the treatment of *non-antigen-presenting cells* with such combinations. Thus, Applicants respectfully contend that there is no disclosure in Trinchieri that anticipates the presently claimed invention.

The Examiner's point in the last paragraph of page 15 of the present Office Action also is incorrect. The Examiner attempts to rebut Applicants' arguments regarding acquisition of antigen-presenting capabilities by HL-60 cells by stating that such a feature is "not recited in the rejected claims." Of course, this feature is *expressly* recited in the rejected claims -- the claims are drawn to treating "antigen-presenting



cells" with combinations of retinoids and cytokines. Hence, the feature of antigen presentation is an express element of the present claims, and the Examiner cannot simply dismiss Applicants' arguments regarding the lack of this limitation in Trinchieri by relying on an erroneous legal standard.

Furthermore, because claim 10 depends from claim 1, Trinchieri *et al.* cannot anticipate claim 10. As a rule, a dependent claim is "construed to incorporate by reference all the limitations of the claim to which it refers." 35 U.S.C. § 112, paragraph 4 (BNA 2001); *see also Bloom Eng'g Co. v. North Am. Mfg. Co.*, 129 F.3d 1247, 1250, 44 USPQ2d 1859, 1861 (Fed. Cir. 1997). Hence, because the "antigen-presenting cell" element in claim 1 is not met by the disclosure of Trinchieri, the recitation of this same element in claim 10 also cannot be met by this reference.

In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) over Trinchieri *et al.* is respectfully requested.

***V. The Rejections Under 35 U.S.C. § 103(a)***

***A. Dunlop et al. and Zhou et al., or Hausser et al. or Cumberbatch et al.***

At page 16, paragraph 10 of the Office Action, the Examiner rejects claims 1-2, 10 and 16 under 35 U.S.C. § 103(a) as being unpatentable over Dunlop *et al.* in view of Zhou *et al.*, or Hausser *et al.* or Cumberbatch *et al.* The Examiner states that Dunlop *et al.* teach a method of modulating the immune system by affecting the physiology of an antigen-presenting cell, and that the invention of claim 1 differs from the teaching of Dunlop *et al.* only in that the method comprises contacting said antigen-presenting cell with an effective amount of at least one retinoid and one cytokine. The Examiner also states that the invention of claim 10 differs from Dunlop *et al.* only in the method

wherein the cytokine is TNF $\alpha$  or IL-1 $\beta$ . The Examiner states that Hausser *et al.* teach that treating monocyte-derived dendritic cells with TNF or soluble CD40L leads to enhanced MHC and accessory surface antigen expression with significantly elevated T cell stimulatory activity, and that Cumberbatch *et al.* teach that intradermal administration of TNF $\alpha$  or IL-1 activate epidermal Langerhans cells, characterized by the acquisition of a more dendritic morphology and the increased expression of Ia molecules. According to the Examiner, Cumberbatch *et al.* also teach that both IL-1 $\beta$  and TNF $\alpha$  can each stimulate the migration of epidermal Langerhans cells. The Examiner concludes that it would have been obvious to one of ordinary skill in the art to modulate the immune system as taught by Dunlop *et al.* by including cytokines as taught by Zhou *et al.*, Hausser *et al.* or Cumberbatch *et al.* The Examiner restates the purported teachings of the cited art as motivation to combine the art. Further, the Examiner states the strongest rationale for combining references is a recognition, expressly or implicitly, in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination. Applicants respectfully disagree with these contentions and traverse the rejection.

Dunlop *et al.* and Zhou *et al.*, or Hausser *et al.*, or Cumberbatch *et al.*, provide no suggestion or motivation to one of ordinary skill to combine their disclosures, nor is there knowledge generally available to those of ordinary skill in the art that provides such motivation or suggestion. There is also no express or implicit suggestion of a reasonable likelihood of success in making or using the claimed invention as a result of combining the cited references. Furthermore, there is no express or implicit recognition drawn from a convincing line of reasoning based on established scientific principles or

legal precedent that some advantage or expected beneficial result would have been produced by their combination. The Examiner has taken selected portions of isolated disclosures and reconstructed them in an attempt to render the claimed invention obvious. One of ordinary skill in the art would not have reconstructed the claimed invention based on the combination of the references cited without using knowledge gleaned from the Applicants' disclosure. This is impermissible hindsight reconstruction that fails to establish a *prima facie* case of obviousness.

In view of the foregoing remarks, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) over Dunlop *et al.* and Zhou *et al.*, or Hausser *et al.*, or Cumberbatch *et al.* be reconsidered and withdrawn.

***B. Dunlop et al. and Zhou et al., or Hausser et al. or Cumberbatch et al. and further in view of U.S. Patent No. 5,552,271***

At page 14, paragraph 20 of the Office Action, the Examiner rejects claims 4-5 under 35 U.S.C. § 103(a) as being unpatentable over Dunlop *et al.* in view of Zhou *et al.*, or Hausser *et al.* or Cumberbatch *et al.* as applied to claims 1-2, 10 and 16 and further in view of U.S. Patent No. 5,552,271 to Pfahl *et al.* According to the Examiner, claim 4 differs from the combined teachings of the references only in that the retinoid is a pan-RXR agonist and an RAR antagonist, and claim 5 differs only in that the pan-RXR agonist is SR11237. The Examiner states that it would have been obvious to one of ordinary skill in the art to substitute the retinoid as taught by Dunlop *et al.* for the various retinoids taught by the '271 patent in combination with the various cytokines as taught by Zhou *et al.*, Hausser *et al.* or Cumberbatch *et al.* The Examiner restates the purported

teachings of the cited art as motivation to combine the art. Applicants respectfully traverse the rejection.

For the reasons discussed above, there is no suggestion or motivation in the cited references that would have led one of ordinary skill to combine Dunlop *et al.* and Zhou *et al.*, or Hausser *et al.*, or Cumberbatch *et al.* or the '271 patent, and that would also suggest a reasonable likelihood of success in making or using the claimed invention as a result of that combination. The Examiner again uses impermissible hindsight reconstruction to combine unrelated pieces of art in an attempt to render the claimed invention obvious. Therefore, the Examiner has not met the burden required to sustain a *prima facie* case of obviousness.

In view of the foregoing remarks, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) over Dunlop *et al.* and Zhou *et al.*, or Hausser *et al.*, or Cumberbatch *et al.*, and further in view of the '271 patent be reconsidered and withdrawn.

### **C. Summary**

Applicants submit that, upon careful analysis of the cited references, the skilled artisan would have found no motivation to combine or modify the reference teachings to arrive at a method of modulating the immune system within the scope of the present claims. Neither is there knowledge generally available to one of ordinary skill in the art that would provide the motivation or suggestion to combine the cited references. Finally, even if the cited references could be properly combined (which they cannot), Applicants respectfully assert that these combined disclosures would not have rendered the claimed invention obvious. Accordingly, a *prima facie* case of obviousness has not been

established, and reconsideration and withdrawal of the rejections under 35 U.S.C.

§103(a) is respectfully requested.

***Conclusion***

All of the stated grounds of rejection have been properly traversed. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply, and allowance of all pending claims, are respectfully requested.

Respectfully submitted,

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